

### **Remarks**

Applicants request reconsideration of the above-referenced patent application.

#### **I. Pending Claims**

The Office action indicates that claims 1, 3, 5, 7, and 9-14 are pending. Applicants note, however, that claims 10-13 are canceled. Thus, only claims 1, 3, 5, 7, 9, and 14 were pending as of the October 1, 2004 date of the Office action.

#### **II. Claim Amendments**

Applicants have amended claims 1, 5, 9, and 14; and added new claims 15-26. All the claims, including the amendments and new claims, are shown in the previous section.

Applicants submit that the amendments do not introduce new matter. Specifically:

Claims 1 and 5 have been amended to be directed to preventing or inhibiting melanoma growth, lung carcinoma growth, or hypercalcemia. This amendment is supported by Applicants' specification at, for example, page 15, line 30 to page 16, line 32; and page 106, line 8 to page 107, line 25. New claims 15-20, 25, and 26 are dependent claims that each recite one such condition, and are therefore likewise supported.

New claims 21, 22, and 24 are supported by Applicants' specification at, for example, page 14, lines 24-27; and page 107, lines 12-20.

New claim 23 is supported by Applicants' specification at, for example, page 7, lines 9-10; and page 106, line 29 to page 107, line 20.

Other amendments rephrase the claims, remove redundancies or unnecessary terms, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

Applicants reserve the right to pursue any canceled subject matter and/or any other subject matter disclosed in this application in one or more later-filed divisional and/or continuation applications.

#### **III. Information disclosure statement**

As indicated in the Office action, Applicants submitted a Form 1449 on September 25, 2003. According to the Office action, however, only the following references were in the Patent

Office's file for the parent application: B1, B2, B4, and C2-C5. To ensure that all the references on the Form 1449 are reviewed, Applicants are submitting a new information disclosure statement that includes copies of all the references listed in the Form 1449. Applicants request that the Examiner initial the Form 1449 from that information disclosure statement, and then return a copy to Applicants with the next Office communication in accordance with MPEP §609.

**IV. Response to objection of claims 1, 5, and 9 for misspelling "methotrexate"**

An objection has been raised to claims 1, 5, and 9 for misspelling "methotrexate". Applicants request withdrawal of this objection. Applicants have amended claims 1, 5, and 9 to correct this spelling error, thereby mooted this objection. Applicants thank the Examiner for noticing this error.

**V. Acknowledgment of withdrawal of dependency objection as to claim 9**

Applicants acknowledge that the improper dependency objection to claim 9 in the December 31, 2003 Office action has been withdrawn.

**VI. Response to non-statutory double patenting rejection as to claims 1, 3, 5, 7, and 9-14**

Claims 1, 3, 5, 7, and 9-14 have been rejected under the judicially-created doctrine of obviousness-type double patenting in view of claims 1-100 in U.S. Application Serial No. 10/865,414. Claims 10-13 are canceled. Thus, this rejection is moot as to those claims. As to the remaining claims, Applicants submit that this rejection is premature because those claims have not yet been found to be otherwise allowable. Applicants will provide a terminal disclaimer (to the extent necessary) once the claims have been found to be otherwise allowable.

**VII. Response to rejection of claims 1, 3, 5, 7, and 9-13 under 35 U.S.C. §112 (first paragraph)**

Claims 1, 3, 5, 7, and 9-13 have been rejected under 35 U.S.C. §112 (first paragraph) for lacking enablement as to the recited conditions. Applicants request withdrawal of this rejection.

Claims 10-13 are canceled. Thus, this rejection is moot as to those claims.

As to the method-of-treatment claims (*i.e.*, claims 1, 3, 5, and 7), Applicants have amended the claims to be directed to preventing or inhibiting melanoma growth, lung carcinoma growth, or hypercalcemia. Applicants submit that this amendment moots this rejection as to the method-of-treatment claims. More specifically, Applicants' Tumor Growth Inhibition example on pages 106-107 provides experimental results with respect to two cell lines. The first cell line, M21, is a melanoma cell line. The other cell line, LLC, is a lung carcinoma cell line. The Office action acknowledges that Applicants' specification supports the method-of-treatment claims as to both cell lines. Applicants submit that the results discussed in Applicants' specification at lines 15-32 on page 16 further support preventing or inhibiting hypercalcemia.

As to the pharmaceutical composition claims (*i.e.*, claims 9 and 14), Applicants note that the rejection does not appear to be applicable. After all, there are no conditions recited in these claims. Moreover, Applicants have provided a detailed description that would enable a skilled artisan to prepare and use the claimed compositions, including factors affecting dosages, example dosages, example modes of administration, experimental results illustrating example combinations, etc. *See* Applicants' specification at, for example, page 14, line 3 to page 15, line 28; page 17, line 26 to page 22, line 3; and page 106, line 8 to page 107, line 25.

New claims 15-26 directly or indirectly depend from either claim 1 or 5. Thus, new claims 15-26 are patentable for at least the same reasons as discussed above with respect to claims 1 and 5.

#### **VIII. Response to rejection of claims 1, 3, 5, 7, and 9-13 under 35 U.S.C. §103(a)**

Claims 1, 3, 5, 7, and 9-13 have been rejected under 35 U.S.C. §103(a) as being obvious in view of Ruminski et al. (WO 97/08145) and Remington's Pharmaceutical Sciences. Applicants request withdrawal of this rejection.

As noted above, claims 10-13 are canceled. Thus, this rejection is moot as to those claims.

Claims 1, 3, 5, and 7 are directed to methods of inhibiting or preventing melanoma growth, lung carcinoma growth, or hypercalcemia using compounds having specific structures in combination with specific chemotherapeutic agents. Applicants' specification illustrates the benefits of such combinations at, for example, the discussion of experimental results at page 15, line 30 to page 16, line 32; and the tumor growth inhibition example on pages 106-107. As can

be seen from that disclosure, results from mono-therapies of the compounds alone or the chemotherapeutic agents alone would not have provided any motivation to a skilled artisan to use the recited combinations. It was Applicants who, in accordance with this invention, discovered the added benefits of such combinations. Thus, the claimed methods of using such combinations cannot be obvious in view of the cited references. *See* MPEP §716.02(a) ("greater than expected results are evidence of nonobviousness").

Claim 9 is directed to a composition comprising a combination recited in claim 1. As noted above with respect to the method-of-treatment claims, the benefits of combinations would not have been obvious from the separate ingredients alone. It was Applicants who, in accordance with this invention, discovered the benefits of the combinations. Thus, the claimed combinations cannot be obvious in view of the cited references.

New claims 15-26 directly or indirectly depend from either claim 1 or 5. Thus, new claims 15-26 are patentable over the cited references for at least the same reasons as discussed above with respect to claims 1 and 5.

**IX. Response to request for structure of S448 cited in Nickols, et al.**

The Office action requests the structure of the compound cited as "S448" in Nickols et al. (cited in the October 1, 2004 Office action). The Undersigned is presently consulting with Applicants to determine the structure and its public availability. It is noted, however, that the citation in an abstract of a compound number without the actual structure cannot constitute prior art against the instant patent application as to that specific compound.

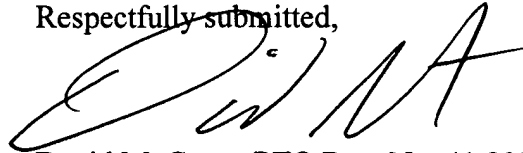
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Applicants hereby request a 3-month extension to respond to the October 1, 2004 Office action. Applicants have enclosed a check to cover the fee for the extension. Applicants believe that they do not owe any additional fee in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

Amendment D  
U.S. Appl. 10/016,146  
April 1, 2005

Applicants submit that the pending claims are in condition for allowance, and request that this application be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

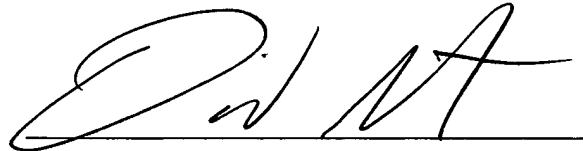
Respectfully submitted,



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**CERTIFICATE OF MAILING UNDER 37 CFR § 1.8**

I certify that this correspondence is being deposited with the U.S. Postal Service on **April 1, 2005** with sufficient postage as first class mail (including Express Mail per MPEP §512), and addressed to **Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450**.



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